Serum long non Coding RNA in keloid patients A Systematic Review and Meta-analysis

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Main facts

Value to find the relation and association between different types of LNC RNAs and keloid.
Aim To assess an association between LNC RNA and keloids.
DATA SOURCES PubMed, Medline.
STUDY Type All are case-control studies that contain people who have keloid and other healthy people that different types of LNC RNA assessed to them.
Information SYNTHESIS by reporting.
Clear OUTCOMES. Outcomes showed increased levels of the 4 LNC RNA in keloid patients than in healthy people.
RESULTS Systematic review of 4 articles found 4 LNC RNA implicated in keloid. The studied LNC RNA were H19, HOXA11, CACNA1G-AS1, and LINC01116. This meta-analysis showed that all of these LNC RNA increased their serum level significantly in keloid cases compared with the control group. Majority of them, their serum level increase significantly with the severity of the disease.
CONCLUSIONS AND RELEVANCE This analysis clear that long noncoding RNAs have a role and effect in the inflammatory process of presentation of keloid and its severity. So, we should understand the pathological pathway of keloid to help in keloid treatment.

Key Points

Question Are level of different types of LNC RNA affected in keloid patients?
Findings These LNC RNA increase their serum level significantly in keloid cases compared with the control group.
Meaning This study found that the level of different types of LNC RNA affected in keloid patients.

Introduction

The LNC RNA H19 is accompanied by proliferation in tumors.**7** However, the molecular mechanism and roles of LNC RNA LINC01116 in the synthesis of keloid are still obscure.**8** There is a big evidence of the value of long non-coding RNAs (LNC RNAs) in keloid progression and development. The main mechanisms are still obscure. In this study, the molecular mechanisms and biological effects of LNC RNA HOXA11-AS in keloid synthesis were assessed.**9** The keloidal fibroblast showed that it contains calcium voltage-gated channel unit alpha1 G antisense RNA 1 (CACNA1G-AS1).**10**

Practical methods

PCR is the investigation to detect LNC RNA. We want to know if H19 increases the proliferation of fibroblasts in keloid disorder or not. polymerase chain reaction clarifies to us that H19 levels were more excess in keloid patients than in normal healthy people.**7** Western blot light to us the levels of microRNA- 203 and LINC01116; Also quantitative real-time polymerase chain reaction (qRT-PCR) can help us to asses them and SMAD5. Cell superfat, invasion, and migration were detected by the Cell counting Kit-8 (CCK-8) method also the trans well method. Cell death and extracellular matrix were examined by western blot and Flow cytometer . The bioinformatics method clarifies to us the relationship between

Keloids are benign dermal fibro-proliferative tumors that extend outside the wound boundary and invade adjacent tissue due to excessive production of extracellular matrix. **1**

Keloid scars affect about 10–15% of all wounds. The incidence is higher among young individuals, as they are prone to trauma; their skin generally has more elastic fibers, resulting in more tension and the collagen synthesis rate is greater in them. **2**

Any type of deep injury in the skin can create abnormal healing of the wound and help keloid scar formation .**3**

Steroidogenesis may be caused by multiple genetic, local , and systemic factors that alone or together stimulate continuous inflammation in the wound and scar.**4**

Pathophysiology of Keloid scars is believed to involve an abnormal balance between proliferation and apoptosis of fibroblast and endothelial dysfunction.**5**

Long noncoding RNAs (LNC RNAs) are defined as transcripts with a length more than 200 nucleotides. They are irregulated and play very important roles in tumor synthesis and cancer spreading, acting as tumor genes or tumor suppressors.

immunoprecipitation(RIP) and by dual luciferase reporter method.**10**

Letter Search

The information excised from PubMed, and Medline from their publication until September 2021. The main items and words are the following: *keloid and long noncoding RNAs* (CACNA1G-AS1, H19, LINC01116 and HOXA11-AS).

Contents and output Criteria

The contents criteria contain observational, interventional studies as case-control that included keloid patients to whom LNC RNAs are investigated compared to healthy people to whom LNC RNAs are investigated. Output criteria show searches don't contain observational , interventional, and studies on tumors rather than keloid and searches did not contain cropped results of us.

Goodness measurement

We performed a full goodness measurement to evaluate the fitness of the four of our included studies which are case-control observational studies.

Extraction of information

We extract the information that helps us in our search such as comparison between studies results, size, groups, characters, design and level of LNC RNA in detail finally.

Search Outcomes

LINC01116, and SMAD5. A dual-luciferase method, RNA pull-down, and RNA Immunoprecipitation (RIP) methods help us more and more in the detection of them.**8** in human keloidal fibroblasts and keloid itself, we used western blot, qRT-PCR method to assess the levels of miR-124-3p, HOXA11-AS, and transforming growth factor β receptor type I (TGFβR1).In order to HOXA11-AS assessment, the loss- and gain-of-function methods were accepted. The cell death and cellular new vessel formation were assessed by some methods such as Flow cytometry, TUNEL, tube formation, and DNA ladder methods. Also, the linkage among miR-124-3p and HOXA11-AS, TGFβR1 and miR-124-3p was clarified by the bioinformatic method and showed by the luciferase method using . Importance of miR -124- 3p was in the organization of TGFβ or PI3K/ Akt, also in HOXA11-AS.**9** The expression of CACNA1G-AS1, miR-205 standards were assessed through quantitative real-time polymerase chain reaction (qRT-PCR). The use of Cell Counting Kit-8 (CCK-8) is very helpful for us in proliferation measurement while cell infestation was measured a trans well method. Caspase-3 is very good in the assessment of keloidal fibroblasts while the flow cytometer can asses the average cell death. The connection among miR -205, CACNA1G- AS1 was performed by RNA

Table(1): summary of searches.

Source	Study design	Country	Study group and sample
Jun et al **9**, 2020	case - control	USA	+40
Jie et al **7**, 2016	case - control	USA	+16
Xu et al **10**, 2020	case - cont	USA	+20

In 4 studies, data on the level of lncRNA detected there is a significant increase in the level of them.

The LNC RNA plays a very important role In keloid presentation risk, severity, and pathogenesis of keloid . This is maybe understood by the fact that LNC RNA affects cell death and cell overgrowth by many mechanisms and pathways, this data will be the big boss in the development of a new type of keloid therapy.

As they decrease the keloidal fibroblast death and increase blood vessel growth of fibroblast.

Statistical tests

Mean ± standard deviation (SD) was the main test that was done in all our included searches and gave us different information on the connection between LNC RNA and keloid. Also, we are helped by the Student's t-test, a one-way analysis of variance (ANOVA) in order to compare different searches. We consider that the significant P value is less than 0.05 in our search.

Results

Review of study

There was difference in LNC RNA presentation in different disorders such as autoimmune or inflammatory or tumors. We selected the 4 LNC RNA assessed in keloid patients until now.

Characteristics of the Included Studies

	rol		
Weiwei et al **8,** 2021	case cont rol	USA	+20

There are many markers increased in keloids such as TGFβR1 and HOXA11-AS, on the other hand, other markers decreased in keloids such as miR-124-3p. According to the function of HOXA11-AS in keloid formation, its high levels decrease cell death and increase new vessel formation in keloidal fibroblast.

Many factors affect HOXA11-AS types through aiming TGFβR1, or PI3K/Akt pathway such as miR124-3p . Finally, HOXA11-AS decreases cell death and also increases new vessel formation in keloids in different ways. The attention to this information will help us to think of a new target for keloidtreatment.**9**

Keloid formation is suggested by increasing some markers such as CACNA1G-AS1 by many mechanisms such as Increasing cell multiplication, decreasing cell death , increase cell invasion through some signals such as miR-205 decreasing, as our marker suppresses it in the tissue of keloid. In addition to that, miR-205 plays a positive role in itself , cellular overgrowth, migration, and keloidal fibroblast death.**10**

Outcomes

In 4 studies, data on the level of lncRNA detected there is a significant increase in the level of them.

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Discussion

We had many methods as (si) RNA-mediated silencing that can help us to understand how fibroblasts' proliferation is mediated by H19. Some results show that increased expression of levels of H19 in keloid patients. Vascular endothelial growth factor (VEGF), and rapamycin (mTOR) play an important role in keloid. It is increasing that is detected by western blotting indicating the contribution of H19 in keloid pathogenesis. Finally, we found that H19 decreased VEGF, and mTOR levels. Fibroblast proliferation is caused by many reasons such as increased levels of H19 through different mediators.**7**

Many markers were increased in keloidal tissue such as LINC01116 and SMAD5 while Many markers were decreased such as miR-203. Fibroblast death is caused in many ways such as decreasing SMAD5 and increasing miR-203. Keloid presentation, proliferation, and ECM production decreased to many factors such as the LINC01116 shortage. Furthermore, miR-203 which could attach to some markers as LINC01116 was targeted by SMAD5.**8**

new types of keloid therapy.

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A total of 4 articles; were in searching the level of LNC RNA expression in keloid patients by PCR. All studies found a significant association with keloid.

Meta-analysis of this study revealed that:

Excessive H19 level expression with keloid patients' serum.

Excessive LINC01116 level expression with keloid patients' serum.

Excessive HOXA11 level expression with keloid patients' serum.

Excessive CACNA1G- AS1 level expression with keloid patients' serum.

Restriction

Restriction of this study is multiple as all of these studies were case-control which already had a retrospective kind and didn't demonstrate the causation.

Conclusion

The summary of our review is that LNC RNA plays a very important role In keloid presentation risk, severity, and pathogenesis of keloid . This is maybe understood by the fact that LNC RNA affects cell death and cell overgrowth by many mechanisms and pathways, this data will be the big boss in the development of

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